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Catarina Castro Vieira

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NOME

CATARINA CASTRO VIEIRA

CARTÃO DE CIDADÃO OU PASSAPORTE (se estrangeiro)	E-MAIL	TELEFONE OU TELEMÓVEL
13780343	catarina.cv.16@gmail.com	917292721

NÚMERO DE ESTUDANTE	DATA DE CONCLUSÃO
200803364	20/03/2014

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Laparoscopic versus open surgery for rectal cancer : oncologic outcomes

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Para os meus pais e irmão

LAPAROSCOPIC VERSUS OPEN SURGERY FOR RECTAL CANCER: ONCOLOGIC OUTCOMES

CATARINA CASTRO VIEIRA

Faculdade de Medicina da Universidade do Porto - Rua Doutor Plácido da Costa 4200-450 Porto, Portugal

catarina.cv.16@gmail.com

DR. FRANCISCO ALEXANDRE VIDAL PINHEIRO CUNHA MONTEIRO

Hospital de São João - Alameda Professor Hernâni Monteiro, 4200-319 Porto, Portugal

francisco.cunha.monteiro@gmail.com

Corresponding author

Name: Catarina Castro Vieira

Address: Rua da Cruz Vermelha nº 17 4715-176 Braga, Portugal

Email: catarina.cv.16@gmail.com

Phone Number: +351 917292721

ABSTRACT

Laparoscopic surgery has proved to be a safe option in the surgical treatment of colon cancer, with better short-term results and similar oncologic outcomes when compared to conventional surgery. However, there has been some skepticism towards the use of laparoscopy to treat rectal cancer, particularly regarding long-term oncologic outcomes. Two central setbacks are the demanding surgical techniques and the lack of prospective randomized clinical trials. This review presents the current evidence regarding the oncologic outcomes achieved with laparoscopy versus laparotomy for the treatment of rectal cancer, including conversion, local recurrence, positivity of circumferential margins, lymph node harvest, and overall and disease-free survival rates.

Conversion rate varied widely among studies, from 0 to 34%, with lower rates reported by more recent studies. Local recurrence, surgical margins positivity and lymph node harvest rates were similar in both surgical techniques. Some studies reported higher survival rates with laparoscopy, while others reported laparotomy advantage. However, these differences were not statistically significant and none of the studies reported a clear domain of one surgical technique over the other.

Concerns about compromise of long-term oncologic outcomes are not supported by current literature. Expert hands and appropriate patient selection are certainly key factors - laparoscopic may not be suitable for all rectal cancers, but it could be safe and successful in selected patients when performed by experienced surgeons.

Results of ongoing trials (COLOR II, ACOSOG-Z6051 and COREAN) are eagerly awaited to define the role of laparoscopic resection for the treatment of rectal cancer.

KEY WORDS

Laparoscopic surgery; Rectal cancer; Total mesorectal excision; Oncologic outcomes

1. INTRODUCTION

Colorectal cancer is one of the most frequent cancers worldwide, with 1,2 million new cases and 608700 deaths in 2008, and being surgery the cornerstone of its treatment, it is not complicated to understand that the surgical techniques may have an especially significant impact on the oncologic outcomes.

Laparoscopic approach became attractive for its potential in reducing surgical trauma while maintaining oncologic outcomes. Studies evaluating the impact of the surgical approach have verified a decrease in blood loss during surgery, less post-operative surgical pain (reduced consumption of analgesic medication), earlier return of bowel function, and shorter length of hospital stay, offering safe and esthetically pleasing alternatives to conventional methods at the same time. Major surgery induces surgical stress with increased demands on patient's reserves, and major inflammatory and immunological responses are triggered. Besides that, trauma causes endocrine and metabolic changes as well. Laparoscopy, by reducing surgical trauma, could attenuate those responses. This could begin to explain the reduced postoperative morbidity associated with this surgical approach. [1] For all these reasons, laparoscopic surgery has become the gold-standard for many procedures over the past decade. [2]

Laparoscopy surgical techniques have been performed to treat colorectal cancer for more than two decades, as the first publications of laparoscopic application to the treatment of colon cancer date from 1991. [2] Port-site metastasis and incomplete oncologic clearance instantly became two main concerns and challenged the safety of laparoscopic procedures.

Recent studies show a minimal port-site recurrence rate (<1%), comparable to open surgery, and defend that, in this setting, the way of handling the specimen extraction has more influence than the surgical approach. Therefore, laparoscopic surgery is now considered to be safe in this regard. [3,4]

Large comparative studies and multiple prospective randomized control trials have demonstrated not only the short-term benefits of laparoscopy in the treatment of colon cancer, as they did before for other laparoscopic procedures, but also equivalent oncologic outcomes. [5-8]

The Clinical Outcomes of Surgical Therapy (COST) and the COlorectal cancer Laparocopic or Open Resection I (COLOR I) trials were two large randomized clinical trials that randomly assigned 872 and 1248 patients, respectively, with colon cancer to either a laparoscopic or an open surgery group, and compared long-term outcomes between them, such as overall survival, disease-free survival and recurrence rates. There were no significant differences between the two surgical approaches in both studies. The absence of oncologic risk and the confirmation of the short-term benefits of laparoscopic surgery suggested that this approach could be feasible and become the gold standard for colon cancer treatment. [6,7]

The Medical Research Council Conventional versus Laparoscopic-assisted Surgery in Colorectal Cancer (MRC CLASICC) trial was the only prospective randomized clinical trial to the date of its publication to include rectal cancer. Seven hundred and ninety four patients were randomly allocated to the laparoscopy or open surgery groups. Similarly to the previously mentioned trials, no differences were recorded between the two groups regarding short-term endpoints and mortality and recurrence rates. Regarding rectal cancer, laparoscopic anterior resection was associated with a higher but not statistically significant circumferential margin positivity rate. A conversion rate of 34% was reported, implying poorer outcomes for those patients. The 3-year, 5-year and 10-year follow-ups of MRC CLASICC trial confirmed the previous results relatively to overall survival and disease-free rates and showed no impact of the slightly higher positivity of circumferential resection on oncologic outcome. The long follow-up results suggest that laparoscopy in colon cancer not only is safe in oncologic terms, but should become the standard treatment. Regarding rectal cancer, results are not yet sufficient to recommend the routine use of laparoscopic resection as the treatment of rectal cancer. [8-11]

Recent reviews summarizing randomized controlled trials information about laparoscopic results in colorectal cancer concluded that laparoscopic colectomy offers short-term postoperative benefits over conventional surgery, and that there is no justification not to recommend it to patients with colon cancer of any stage since the oncologic outcomes are not compromised. [12,13]

On the other hand, as briefly mentioned before, laparoscopic rectal cancer was not welcomed with such enthusiasm. The lack of prospective randomized clinical trials

addressing specifically the comparison between laparoscopy and open surgery for rectal cancer is an important drawback when examining long-term oncologic outcomes.

This review presents the current evidence regarding the oncologic outcomes achieved with laparoscopy versus open surgery for the treatment of rectal cancer.

2. LAPAROSCOPY IN RECTAL CANCER

2.1. TOTAL MESORECTAL EXCISION: LAPAROSCOPIC TECHNIQUE

Total mesorectal excision (TME) has been widely adopted for rectal cancer surgery over the past years, after having accomplished improved outcomes, particularly in regard to local recurrence, since it was introduced by Heald and Ryall during the 1980s. Some studies concluded that this procedure has reduced recurrence rates from between 30% and 40% to 5%. [14]

The surgical technique provides excision of the intact mesorectum, and en bloc removal of the rectum and the tumor prevents micrometastases to remain in place. Posterior sharp dissection of the loose areolar tissue between the presacral fascia and the investing fascia of the mesorectum and anterior dissection performed through the Denonvillier's fascia between the rectum and the prostate or posterior wall of the vagina, in men and women, respectively, are two important steps to accomplish complete mesorectum excision. Other TME principles include high ligation of the inferior mesenteric vessels (it facilitates mobilization of the splenic flexure and laparoscopic dissection in the anatomic planes, and could prevent potential intravascular dissemination of cancer cells during manipulation) and excision of the distal mesorectum of not less than 5 cm (in distal rectal cancers, a negative distal margin of 1 to 2 cm may be acceptable); this should be confirmed to be tumor-free by frozen section. [15,16]

Laparoscopic TME is not yet internationally standardized, but common surgical steps were adopted by several groups of surgeons. Leroy *et al* described the laparoscopic technique in 2002, and since then it has been used by many institutions. It proceeds as follows. Colorectal mobilization, vessel ligation, transaction and anastomosis are performed entirely laparoscopically. Five to six trocars measuring 5 to 12 mm are placed and excessive mobility is avoided by placing a suture to anchor the trocar to the abdominal wall. High ligation of the inferior mesenteric artery at its origin from the aorta with preservation of the left colic artery and lymphatic clearance of all lymph nodes at the base of the same artery are performed. The next step includes mobilization of the rectum as far down as possible on its posterior and right lateral surfaces before opening the anterior rectal space from right to left, extending from Douglas's pouch.

Complete rectal mobilization is accomplished after freeing the lateral attachments of the sigmoid colon, followed by the rectum, on its left lateral and posterior surfaces. The dissection is then continued down to the pelvic floor, alternating right lateral, left lateral, anterior, and posterior dissection. Sharp dissection between the parietal and visceral planes of the pelvic fascia is then performed to dissect the mesorectum. The pelvic autonomic nervous system, namely the hypogastric nerves and the autonomic branches of S2, S3 and S4 are identified and preserved, if possible. The rectum is completely excised within the visceral pelvic fascia and irrigation of the pelvis is carried out. Coloanal hand-sewn or double-stapling anastomosis can be performed if sphincter preservation is desired and feasible. The specimen is placed in an extraction bag and removed through a small suprapubic Pfannenstiel-type incision, with a plastic wound protector preventing contact. [2,15,16]

Most of the published studies indicate safety and technical feasibility of the laparoscopic approach when performed by expert hands, with reduced perioperative morbidity and lower local recurrence rates, when compared to open TME. [2,15-17]

Moreover, laparoscopy can provide a magnified view of the pelvis anatomy, allowing greater precision and better identification of important structures such as the nervous plexus, significantly aiding in their preservation and improving functional results. [16]

Although technically more demanding, the possibility of faster standardization of the surgical procedure could also become an advantage of laparoscopic TME. [16]

2.2. DIFFICULTIES IN LAPAROSCOPIC RESECTION OF RECTAL CANCER

Laparoscopy techniques in rectal cancer are more challenging than the ones performed for colon cancer. There are specific questions related to rectal anatomy, such as difficult exposure in a narrow pelvis, proximity to nerve structures, difficult intestinal resection, and the need to control longitudinal and lateral resection margins. Especially in case of sphincter-saving TME with low anastomosis, technical issues regarding staplers can ensue, since it might not be feasible to perform a distal resection line in the low rectum exactly perpendicular to the longitudinal axis, and only with an acute angle to this axis. [2,16] Problems with anastomosis and difficulties in rectal transection, narrow pelvis, bulky tumors, adhesions and obesity are among the most common reported reasons for

conversion and can represent relative contraindications to laparoscopy. Studies suggest that the open approach may be more suitable for these patients. [8,15,18-22]

Challenges in this setting also include steep learning curves, longer operative time, concerns about the oncologic outcome, conversion risk and the lack of randomized controlled prospective trials declaring clear domain of laparoscopic over open surgery for rectal cancer treatment. [15,23]

3. LAPAROSCOPIC VERSUS OPEN SURGERY: ONCOLOGIC OUTCOMES

3.1. CONVERSION RATE AND ITS IMPACT ON SURGICAL OUTCOME

Conversion rate records vary widely between studies. (table 1) [8,17-19,21,24-34]

Several factors can influence the rate of conversion, such as the patient's characteristics (age, Body Mass Index (BMI), American Society of Anesthesiology score), intraoperative difficulties and surgeon's experience. As previously mentioned, conversion may be the result of problems with anastomosis and difficulties in rectal transection, narrow pelvis, bulky tumors, adhesions and obesity and, in those cases, an open approach may be more suitable. [8,15,18-21,26]

The impact of conversion on surgical and oncologic outcomes is not completely understood yet and inconsistent results have been published. Some studies defended that conversion rates can result in poorer outcomes, while others found no significant differences in postoperative and oncologic outcomes between laparoscopic and converted patients. [8,15,18,19,21,29,30]

It is critical to keep in mind the importance of completing surgery in an oncologically safe manner over completing it laparoscopically. The decision to convert must be made before there is any compromise of resection margins, in order to prevent condemning a patient to R1 resection and local recurrence. [35]

Yamamoto *et al*, in a retrospective analysis of 1073 patients with rectal carcinoma undergoing laparoscopic surgery, reported a conversion rate of 7,3%. Patients requiring conversion had higher BMI (24,6 versus 22,7; $p<0,001$), higher rates of anterior resections, and higher morbidity rates (43,6% versus 21,1%). This was the first study with a large number of patients to suggest that conversion has negative effects on short-term outcomes in rectal carcinoma. [19]

Rottoli *et al* analyzed data from a prospective database of laparoscopic rectal resection performed in 173 patients with rectal cancer, and found a conversion rate of 15%. Converted (CR) patients had a mean BMI of 27,3 while not converted (NCR) had a BMI of 24,9 ($p<0,001$). The number of patients with stage IV disease was significantly higher among CR patients (26,9% versus 4,8% of NCR patients; $p<0,001$). No

statistically significant differences were reported between groups regarding 5-year overall and disease-free survival. The authors showed a trend toward CR patients having higher overall recurrence rates. In summary, in this study, BMI and stage IV disease were predictor factors associated with conversion, and although conversion did not affect post-operative immediate results, it could have an important impact on long-term outcomes. [18]

Thorpe *et al* stated that male sex could be an important factor for conversion and Laurent *et al* reported a 3-fold higher conversion rate for men with stapled anastomosis. [15]

MRC CLASICC reported, as previously mentioned, a 34% conversion rate, which was reduced in every year of recruitment, reflecting the impact that the learning curve can have on the conversion rate. Patients undergoing conversion had higher in-hospital mortality and complication rates. Conversion was more common among advanced cancers and patients with higher BMI. [8]

In a prospective series of 389 patients with rectal cancer, Strohlein *et al* reported an increase in metachronous metastasis and local recurrence in the converted group, compared with either completed laparoscopic resection or open surgery. [36]

Other studies reported lower conversion rates. Rottoli *et al* and Laurent *et al* registered 15% conversion rates, Law *et al* 12,5%, Lujan *et al* 7,9%, Ng SS *et al* 7,5%, Yamamoto *et al* 7,3% and Li *et al* 5,3%. [18,19,24,27,28,31,32] Of these, Law *et al* registered a not statistically different but suggestive higher rate of local recurrence for those requiring conversion (16,9% versus 6,9%; p=0,108) [28]. Even lower conversion rates have been reported by Leroy *et al* (3%), Tsang *et al* (1,9%) and Bärlehner *et al* (1%). [17,25,34] This could be due to technological advances, surgeon experience, and more careful patient selection, particularly regarding obese patients, anterior resections, and advanced tumors.

Hotta *et al* selected studies with a large number of patients undergoing laparoscopic surgery published between 2000 and 2009 and noticed a range of 1% to 21,9% regarding conversion rate. [21] Two meta-analyses, including only randomized clinical trials, also found a significant range regarding conversion rate, from 0% to 34%. [29,30]

The COLOR II randomized clinical trial reported recently its short-term outcomes and the conversion rate reported was 17%. The reasons for conversion were similar to the ones mentioned before. [26]

TABLE 1 – CONVERSION RATES

STUDY	**TYPE OF STUDY**	**NUMBER OF PATIENTS**	**CONVERSION RATE, %**
MRC CLASICC [8]	RCT	L=242	34,0
Ng SS *et al* [29]	RCT	L=76	30,0
Morino *et al* [29]	Nonrandomized comparative study	L=98	18,4
COLOR II [26]	RCT	L=699	17,0
Laurent *et al* [27]	Retrospective comparative study	L=238	15,1
Rottoli *et al* [18]	Case series	L=173	15,0
Law *et al* [28]	Nonrandomized comparative study	L=111	12,5
Ng SS *et al* [33]	RCT	L=51	9,8
Lujan *et al* [31]	RCT	L=101	7,9
Ng SS *et al* [32]	RCT	L=40	7,5
Yamamoto *et al* [19]	Case series	L=1073	7,3
Braga *et al* [29]	RCT	L=83	7,2
Ng KH [29]	Case series	L=579	5,4
Li *et al* [24]	Nonrandomized comparative study	L=113	5,3
Leroy *et al* [17]	Case series	L=102	3,0
Tsang *et al* [34]	Case series	L=105	1,9
Bärlehner *et al* [25]	Case series	L=194	1,0

RCT=randomized clinical trial; L=laparoscopy

3.2. SURGICAL MARGINS, LYMPHADENECTOMY AND LOCAL RECURRENCE RATES

Since the introduction of laparoscopy in the treatment for colorectal cancer that one of the main concerns was whether it provides rectal excision equivalent to the open procedure, with adequate lymphadenectomy and radial and circumferential clearance in order to avoid recurrence of cancer.

As previously mentioned, TME excision has reduced the local recurrence rate in a remarkable way and, at present, it is considered equivalent to open TME.

Negative surgical margins are crucial to avoid local recurrence. Circumferential margin positivity is considered an independent factor in local recurrence. [15,16] Radial margins <2cm are related to a 16% local recurrence rate, contrasting with a 6% rate if the radial margin is >2cm. [16,37] The distal resection margin is still controversial, but most surgeons consider a 2 cm distal margin acceptable. [15]

The number of lymph nodes (LN) harvested during surgery varies widely. For a correct pathological staging, removal of 12 LN is advised, but most series report lower number of harvested LN. This could be due to the chemoradiotherapy regimens that are applied. However, high ligation of the inferior mesenteric vessels, which is now performed in laparoscopic TME, can help improve node harvest, allowing more accurate tumor staging. [15,16]

Several meta-analyses and reviews report no difference between the two surgical approaches concerning the mean number of LN removed. [2,29,30,36,38] The meta-analysis published by Anderson *et al*, which had 17 publications reporting the number of LN harvested, stated, however, open surgery advantage (12 LN versus 10 LN). [37] Lujan *et al* and Ng SS *et al*, on the other hand, showed laparoscopic advantage. [31,32]

The MRC CLASICC trial reported similar LN harvest and positivity surgical margins rates in laparoscopic and open surgery groups, except in laparoscopic anterior rectal resection, where slightly higher but not statistically significant positive circumferential margin rates were verified. [8] However, the 3-year analysis of the same clinical trial showed no impact of that finding on oncologic outcome, including local recurrence rates. [9] These were comparable between the two surgical approaches (7,8% in laparoscopic resection and 7% in open surgery). [8] Surgeons in their learning curve, not standardized preoperative chemoradiotherapy and advanced tumors could have contributed to the initial alarming results. [8] Similarly, Laurent *et al* found non-significant higher circumferential margin positivity rates associated with laparoscopic approach, in a retrospective comparative study that focused on intersphincteric resection for low rectal cancer. Possible explanations for this fact are the more distal nature of tumors and also the more frequent involvement of the internal sphincter in the laparoscopic group. [39] On the other hand, Lujan *et al*, in a recent large prospective multicentre analysis of 4970 patients, reported significantly higher circumferential and

distal margin involvement in the open group, although it did not affect local recurrence and survival after a follow-up of 22 months. [40]

Kirzin *et al* showed similar invasion of distal and circumferential resection margins for both procedures, which is comparable to previously reported results of Huang *et al* and Ohtani *et al*, and Anderson *et al* and Gao *et al* respectively. [2,29,37,38] Anderson *et al* published circumferential margin positivity rates of 5% and 8% and distal margin positivity rates of 1% and 0,6% for laparoscopy and open approach, respectively. In what concerns margin distance, there were not significant differences registered as well. These values are comparable to other meta-analyses. [37]

Local recurrence rates have not ranged wildly between studies and were similar between laparoscopic and open surgery. [13,17,24,26-28,31,37]

As previously mentioned, MRC CLASSIC reported rates of 7,8% and 7% for laparoscopic and open surgery, respectively. [8] Laurent *et al* revealed no difference between open and laparoscopic rectal excision concerning recurrence rates at five years (5,5% versus 3,9%; p=0,371) in a retrospective comparative study in which 233 patients with rectal cancer were treated by open surgery and 238 by laparoscopy. [27] Law *et al*, who compared the outcome of open and laparoscopic resection for stage II and III rectal cancer, found no differences in local recurrence rates. [28]

Lujan *et al*, in a single centre randomized controlled trial in which 204 patients with middle and low rectal cancers were randomized to either open or laparoscopic resection, found rates of 5,3% and 4,8% of 5-year local recurrence, respectively. [31] Li *et al* also focused on middle and low rectal cancers, and reported no differences between laparoscopy and laparotomy regarding surgical margins, LN harvest, and local recurrence rates at 5 years (9,1% versus 6,4%, respectively). [24]

Leroy *et al* reported a rate of local recurrence of 6%. All but one of the pelvic recurrences occurred in node-positive patients and all but one in patients who had received preoperative radiotherapy. This reflects the influence that other factors can have in local recurrence rates. Previously reported risk factors include N2 disease, perineural invasion and positive lateral margins. [17]

A multi-institutional series from Japan regarding 1057 patients that underwent laparoscopic resection of rectal cancer reported a slightly lower local recurrence rate of 1%. [20]

Anderson *et al* published overall local recurrence rates of 7% for laparoscopic and 8% for open resections in their meta-analysis of 24 studies. [37] The Cochrane systematic review of laparoscopic versus open TME for rectal cancer, published in 2006, reported similar local recurrence rates (7,2% versus 7,7%). [13]

Recently published COLOR II trial results also showed no difference between laparoscopic and open surgery regarding proximal margins and positive circumferential resection margins after surgery for cancer located in the upper portion of the rectum. For low rectal cancer resection, laparoscopy allowed a lower rate of positive margins. [26]

3.3. OVERALL AND DISEASE-FREE SURVIVAL

In the MRC CLASICC trial, the overall survival was not influenced by the stage disease and rates were similar between the two surgical approaches, but conversion to laparotomy had a negative impact on the outcome. Five-year overall survival rates for conversion, laparotomy and laparoscopy were 49,6%, 58,5% and 62,4%, respectively (p=0,005). [10] Long-term results confirmed worse overall survival for converted patients (59,2 versus 78,4 and 94,8 months, respectively, p=0,001). [11] In contrast, in the study of Laurent *et al*, survival was not influenced by conversion. Cancer-free survival at 5 years was 82% and 79% after laparoscopy and laparotomy, respectively (p=0,52) and no difference according to tumor stage was noted. By contrast, 5-year overall survival was higher in the laparoscopic group (83% versus 79%) and this difference, although not statistically significant, was more pronounced in stage III cancers (78% versus 70% P=0,279). [27]

Law *et al* also registered improved survival in the laparoscopic group. Five-year survival rates were 71,1% and 59,3% in the laparoscopic and open groups, respectively (P=0,029). [28] The same authors carried out another study that aimed to compare the overall and disease specific survivals of laparoscopy and laparotomy, to confirm previous findings in a cohort of larger number of patients with longer follow-up.

Laparoscopy was one more time associated to better survival rates, particularly in cancer stages II and III. [41] It was suggested in this study that the improved survival associated with laparoscopy could be due to a better immunologic response. In fact, lower levels of tumor necrosis factor alpha, interleukin 1-6, vascular endothelial growth factor and C-reactive protein, which are responsible for the postoperative inflammatory response, have been associated with laparoscopy for some time. [1,41]

Morino *et al* also noted a significantly longer cumulative survival for patients with more advanced cancers (stage III or IV) treated with laparoscopic surgery but it was the only individual author to do so in a meta-analysis by Anderson *et al*, who published a mean overall survival based on 13 studies of 72% for laparoscopic resections and 65% for open surgery at a mean follow-up period of 4,4 years (p=0,5). [37]

Besides MRC CLASICC trial, other trials showed no difference between the two surgical approaches. Among them are the trial by Lujan *et al* (72,1% versus 75,3% for laparoscopy and laparotomy, respectively); the multicenter retrospective Japanese study involving 1057 patients; a comparative prospective study by Li S *et al* (77,9% versus 78,9% at 5-years for laparoscopy and laparotomy, respectively) and a Chinese randomized clinical trial that analyzed 1-year, 2-year and 3-year survival rates. [21,24,31,42] Ng SS *et al*, in a small randomized trial involving 80 patients, published 5 and 8-year overall survival rates of 85,9% and 82%, and 91,3% and 72,7% in laparoscopic and open surgery, respectively. These rates were similar between surgical approaches as well, but were slightly better than the ones reported by other trials. However, this finding could be due to the exclusion of abdominoperineal resections from the study. [32]

A meta-analysis including six randomized controlled trials and 1033 patients also reported similar rates (p=0,11) in overall and disease-free survival. [38]

Few studies have reported 5-year survival data. Most follow-ups are shorter than that, and longer-term outcomes are awaited. Some trials show better survival rates in the laparoscopic group, others in the open surgery group, reflecting inconsistency between studies. However, these differences are not statistically significant and none of the studies previously mentioned reported a clear domain of one surgical technique over the other.

3.4. ONGOING TRIALS

3.4.1. COLOR II

COLOR II is the largest randomized trial to compare laparoscopic and open surgery for rectal cancer. This study was carried out between January 20, 2004 and May 4, 2010. Of the 1044 patients from 30 hospitals and centers in 8 countries available for analysis, 699 were randomly assigned to laparoscopic surgery and 345 to open surgery (ratio 2:1). Patients with distant metastasis, T3 cancers within 2mm from the endopelvic fascia and T4 cancers were excluded. The primary endpoint in this trial was local recurrence at 3 years, and secondary endpoints the short-term results, including operative findings, complications, mortality and pathological examination (completeness of the resection, surgical margins and number of harvested lymph nodes).

The information concerning short-term outcomes was published recently. The authors concluded that the laparoscopic approach can achieve similar rates of intra-operative complications, morbidity and mortality. No difference was recorded between groups regarding proximal and circumferential resection margins positivity after surgery for cancer located in the upper portion of the rectum. For low rectal cancer resection, laparoscopy allowed a lower rate of positive margins. Long-term results on local recurrence and survival rates are awaited. [26]

3.4.2. ACOSOG-Z6051

This American study began in August 2008 and is a phase 3, prospective randomized clinical trial involving 650 patients. It compares laparoscopic-assisted resection with open surgery for rectal cancer, and its primary endpoint is to show that laparoscopy is not inferior to open resection in patients with stage IIA, IIIA or IIIB rectal cancer, regarding circumferential and distal margins and completeness of TME. Secondary endpoints include local recurrence and disease-free survival rates, and functional outcomes. [15]

3.4.3. COREAN

This trial was carried on from April 4, 2006 to August 26, 2009 and it was designed to assess the safety of laparoscopy compared with conventional surgery for mid and low rectal cancer after chemoradiotherapy. Patients with cT3N0-2 mid or low rectal cancer

without distant metastasis were included in the study and randomized to receive open (n=170) or laparoscopic surgery (n=170). All patients received a fluoropyrimidine-based chemoradiotherapy regimen preoperatively. The primary endpoint is 3-year disease-free survival. Secondary endpoints include involvement of the circumferential resection margin, number of harvested LN, and macroscopic quality of the TME specimen.

LN harvest, proximal distal and radial resection margins, as well as circumferential resection margin positivity and macroscopic quality of TME specimen were similar between groups. Conversion rate was 1,2%. This trial was the first randomized trial focusing on the impact of preoperative chemoradiotherapy regimens, and it shows feasibility and safety of the laparoscopic procedure in expert hands after chemoradiotherapy, without jeopardizing short-term oncologic outcomes. Patients continue to be followed-up to assess 3-year disease-free survival. [43]

4. DISCUSSION

Laparoscopic surgery has proved to be a safe and feasible option in the surgical treatment of colon cancer, with better short-term results and similar oncologic outcomes when compared to conventional surgery. However, there has been some skepticism towards the use of the laparoscopic approach to treat rectal cancer, particularly regarding long-term oncologic outcomes. If these are not proven to be equivalent or better than the ones open surgery has to offer, the short-term advantages will not matter.

A central setback in the acceptance of laparoscopy as a first-line treatment for rectal cancer is the lack of prospective randomized clinical trials with a large number of patients addressing specifically the comparison between laparoscopy and laparotomy and clearly stating the advantage of laparoscopy over open surgery in terms of oncologic outcomes. The bulk of available data comes from relatively small randomized control studies and larger non-randomized case series, since most of the published multicenter trials regarding colorectal cancer did not recruit patients with rectal cancer because the procedure is technically demanding. [13,32]

The heterogeneity of protocols is an important aspect to consider when drawing conclusions. Follow-up periods varied widely. Exclusion criteria can lead to selection bias. Factors such as the lack of standardization of the surgical technique, type of procedure, localization and stage of the tumor, presence or absence of neoadjuvant and adjuvant radiochemotherapy, patient's characteristics and surgeon's experience can influence outcomes regardless of the surgical approach, and have to enter the equation as results are interpreted. [13]

Oncologic safety can be measured by conversion rate, surgical margins positivity, number of LN harvested, local recurrence and survival rates, and that was the reason why those parameters were analyzed in this review.

Conversion rates ranged widely, from 0% to values as high as 34%, with more recent studies reporting lower rates. This could be due to heterogeneity of clinical trials, different phases of the learning curve, and better patient selection. The most reported reasons for conversion were bulky tumors and obesity. Conversion seems to have a negative impact on surgical outcomes, but some inconsistent results have been

published and this issue is not yet fully understood. Careful preoperative assessment of risk factors for conversion can help prevent it. [8,15,18-22]

MRC CLASICC initially reported alarming results on circumferential surgical margins. However, 3-year outcomes did not show any impact on local recurrence. [8] Although other studies also reported lower rates of margin clearance associated with laparoscopy, these were not statistically significant. Moreover, most meta-analyses showed no difference between surgical approaches. The same happened with LN count and local recurrence rates, which were similar in laparoscopic and open surgery.

Most follow-ups are relatively shorter and long-term survival has been published in very few studies, not allowing definitive conclusions. The survival rates reported have been similar and none of the studies found a clear domain of one surgical technique over the other in this regard.

The surgeons' experience is without doubt a factor with great importance in rectal cancer surgery, since it is technically demanding. Rectal cancer surgery requires more training time than colon cancer surgery, and laparoscopy more than laparotomy. This is why, for many surgeons, open surgery is still the chosen approach for treating rectal cancer. In the MRC CLASICC trial, the learning curve was estimated at 20 cases. [8] Multidimensional analysis of the learning curve for laparoscopic surgery were performed by various authors, and surgeons' experience was related to less operating time, decision to perform protective diverting stoma and surgical site infection rate. [44-46] The reduction of conversion rate and postoperative complications seemed to require higher number of cases, reflecting the need of mastery of the surgical technique by surgeons. [46] Park *et al* also analyzed the impact of surgeons' experience and concluded that the learning curve for oncologic safety was longer. [47] The number of cases required to plateau in terms of speed, morbidity rate, conversion rate and oncologic adequacy remains debatable and varies extensively between studies. [35,44-46]

Recently, some studies have focused on the impact of the combination of fast-track programmes and laparoscopic technique. As they had a dramatic effect on perioperative outcomes in colorectal surgery, rectal cancer patients could be expected to benefit from them in the same manner. By reducing stress and pain with aggressive postoperative mobilization and early oral feeding, the body stress response and organ dysfunction are

reduced to a minimum, thus improving postoperative morbidity and mortality rates. However, the lack of randomized clinical trials addressing these programmes directly does not allow consistent and definitive conclusions. For now, fast-track protocols seem promising. Nevertheless, one must not forget that surgeon's experience is a crucial factor capable of improving outcome in rectal cancer surgery. Probably the combination of advanced surgical techniques and better perioperative care is the way to improve patients' outcome. [23,48,49]

Despite all the setbacks previously mentioned, randomized clinical trials suggest that laparoscopy is a safe, feasible option for the treatment of rectal cancer, offering improved short-term results compared to open surgery, without adversely affecting oncologic outcomes.

Expert hands combined with appropriate patient selection may be the key to withdraw the best possible outcome from laparoscopic surgery. Some believe that the main question is not open versus laparoscopic surgery, but rather how to decide on the most suitable surgical technique for each patient, taking into consideration all the variables that can interfere with oncologic outcome. [50] Laparoscopic may not be suitable for all rectal cancers, but it could be safe and successful in selected patients when performed by experienced surgeons. [35]

Recently, a report from the prospective COST trial concluded that age and tumor stage are the variables with most impact on survival, and surgical quality surrogates (surgical technique, LN count and surgical margins) were not prognostic. Although patients in this study had colon cancer, its conclusions are intriguing, and make one question about their reproducibility in the context of rectal cancer. Besides, it emphasizes the importance of patient selection for laparoscopy which, as previously seen, has a crucial role in rectal cancer surgery. [51]

Concerns about compromise of LN harvest, conversion rate, circumferential margins and overall survival are not supported by current literature. However, there is a paucity of data concerning long-term oncologic outcomes. Results of COLOR II, ACOSOG-Z6051 and COREAN trials are eagerly awaited to define the role of laparoscopic resection for the treatment of rectal cancer.

CONFLICT OF INTEREST STATEMENT

There are no conflicts of interest to report.

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ANEXOS

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